Potential lung disease biomarkers yield clues to COX-2 inhibitor side effects

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In searching for a simple way to identify individuals with smoking-related lung injury, scientists at Weill Cornell Medical College have stumbled upon a potential explanation for why the class of pain-relievers known as COX-2 inhibitors increases the risk of heart problems among users.

The findings are notable in two ways, explains Dr. Andrew J. Dannenberg, director of the Weill Cornell Cancer Center and the Henry R. Erle, M.D.-Roberts Family Professor of Medicine at Weill Cornell Medical College and a leading gastroenterologist at NewYork-Presbyterian Hospital/Weill Cornell Medical Center. "Not only could they lead to the development of a simple urine test to determine which smokers are at increased risk of developing chronic obstructive pulmonary disease or emphysema, but they might also pave the way for new drugs or combinations of drugs that harness the benefit of COX-2 inhibitors, including cancer-fighting properties, with reduced cardiovascular toxicity."

Dr. Dannenberg is senior author of a new study detailing the findings which appears in the April issue of *Cancer Prevention Research*. A collaboration led by Weill Cornell Medical College and Memorial Sloan-Kettering Cancer Center, the research study was funded by Weill Cornell's Clinical and Translational Science Center (CTSC), an NIH-funded consortium for biomedical collaboration on New York's Upper East Side, as well as by the Flight Attendant Medical Research Institute (FAMRI), Pfizer Inc., and a Memorial Sloan-Kettering Cancer Center

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COX-2 inhibitors were developed to selectively target the cyclooxygenase-2 (COX-2) enzyme, which plays an important role in inflammation. The idea was to treat pain and arthritis without the potentially dangerous gastrointestinal side effects of other non-steroidal anti-inflammatory drugs (NSAIDs). This class of drugs has also been shown to reduce colorectal polyps, a precursor to colorectal cancer. But two blockbuster COX-2 inhibitors, Vioxx (rofecoxib) and Bextra (valdecoxib), were pulled off the market after reports that they elevated the risk of heart attack, stroke and death in users. Celebrex (celecoxib) is the only COX-2 inhibitor still available.

The current trial was originally designed to identify biomarkers in urine which could indicate the presence of incipient, smoking-related lung disease. The researchers had hypothesized that early-stage lung injury could "turn on" the COX-2 gene, increasing levels of the major prostaglandin metabolite PGE-M in the urine.

In addition to determining PGE-M levels, the investigators also looked at levels of the biomarker leukotriene E4 (LTE4), formed by the 5-lipoxygenase (5-LO) pathway. Both biomarkers, representing these two different pathways, are synthesized from arachidonic acid. The 5-LO pathway has also been implicated in inflammation, cancer and cardiovascular problems.

For this study, 28 never-smokers, 26 former smokers and 28 current smokers took 200 milligrams of Celebrex twice a day for about a week. At the beginning of the study, current smokers had higher levels of both PGE-M and LTE4 than never-smokers. High PGE-M levels suggest higher levels of COX-2 activity. Twice-daily doses of Celebrex resulted in reduced PGE-M levels in all three groups, with the largest drop seen

among those who had high starting levels of PGE-M.

"But we also found that Celebrex treatment led to increases in urinary LTE4 levels, primarily among individuals who had started out with high PGE-M levels," says first author Dr. Anna J. Duffield-Lillico, a consultant with the Department of Epidemiology and Biostatistics and the Department of and Surgery at Memorial Sloan-Kettering Cancer Center. "This indicated that Celebrex 'shunted' or redirected arachidonic acid into the 5-LO pathway from the COX pathway. When one went down, the other went up." This is important because other studies have suggested an important role for the 5-LO pathway in atherosclerosis, heart attacks and stroke.

And it is this increased shunting of arachidonic acid into the 5-LO pathway that may help explain why COX-2 inhibitors contribute to cardiovascular problems, the researchers say.

"More studies are needed to see if these two biomarkers are reliable indicators of the presence of low-level lung inflammation," notes Dr. Dannenberg.

And more research is necessary to understand the role of COX-2 inhibitors in the heart, especially to see if their anti-cancer effects can be attained without the counterbalancing negative effects.

Source: Weill Cornell Medical College